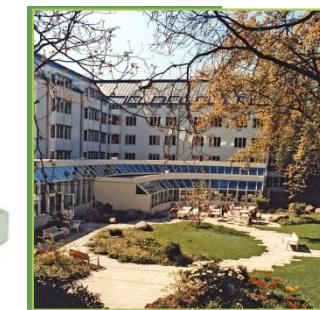




DGHP Symposium: „Strom, Magnet oder Ketamin: Was hilft?“ online, 16. Juni 2021

tDCS zur Therapie der Depression

Prof. Dr. Frank Padberg, Sektion für Psychosomatische Medizin und Psychotherapie
Klinik für Psychiatrie und Psychotherapie, LMU Klinikum, padberg@med.uni-muenchen.de



New! Free Online

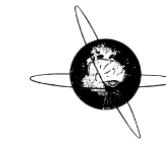
Clinical Neurophysiology 131 (2020) 474–528



Contents lists available at ScienceDirect

Clinical Neurophysiology

journal homepage: www.elsevier.com/locate/clinph



Evidence-based guidelines on the therapeutic use of repetitive transcranial magnetic stimulation (rTMS): An update (2014–2018)



Jean-Pascal Lefaucheur ^{a,b,*}, André Aleman ^c, Chris Baeken ^{d,e,f}, David H. Benninger ^g, Jérôme Brunelin ^h, Vincenzo Di Lazzaro ⁱ, Saša R. Filipović ^j, Christian Grefkes ^{k,l}, Alkomiet Hasan ^m, Friedhelm C. Hummel ^{n,o,p}, Satu K. Jääskeläinen ^q, Berthold Langguth ^r, Letizia Leocani ^s, Alain Londre ^t, Raffaele Nardone ^{u,v,w}, Jean-Paul Nguyen ^{x,y}, Thomas Nyffeler ^{z,aa,ab}, Albino J. Oliveira-Maia ^{ac,ad,ae}, Antonio Oliviero ^{af}, Frank Padberg ^m, Ulrich Palm ^{m,ag}, Walter Paulus ^{ah}, Emmanuel Poulet ^{h,ai}, Angelo Quartarone ^{aj}, Fady Rachid ^{ak}, Irena Rektorová ^{al,am}, Simone Rossi ^{an}, Hanna Sahlsten ^{ao}, Martin Schecklmann ^r, David Szekely ^{ap}, Ulf Ziemann ^{aq}

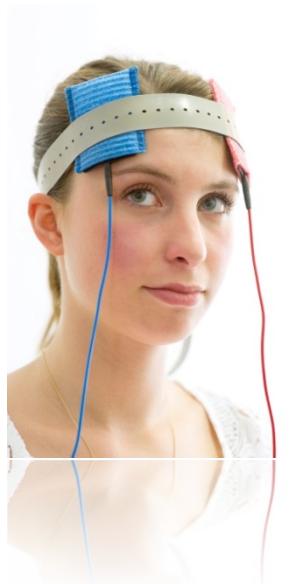
Clinical Neurophysiology 128 (2017) 56–92



Contents lists available at ScienceDirect

Clinical Neurophysiology

journal homepage: www.elsevier.com/locate/clinph



Guidelines

Evidence-based guidelines on the therapeutic use of transcranial direct current stimulation (tDCS)



Jean-Pascal Lefaucheur ^{a,b,*}, Andrea Antal ^c, Samar S. Ayache ^{a,b}, David H. Benninger ^d, Jérôme Brunelin ^e, Filippo Cogiamanian ^{f,g}, Maria Cotelli ^h, Dirk De Ridder ^{i,j}, Roberta Ferrucci ^{f,g}, Berthold Langguth ^k, Paola Marangolo ^{l,m}, Veit Mylius ^{n,o}, Michael A. Nitsche ^{p,q}, Frank Padberg ^r, Ulrich Palm ^r, Emmanuel Poulet ^{e,s}, Alberto Priori ^{f,g,t}, Simone Rossi ^u, Martin Schecklmann ^k, Sven Vanneste ^{v,w}, Ulf Ziemann ^x, Luis Garcia-Larrea ^{y,1}, Walter Paulus ^{c,1}

No. 765,530.

PATENTED JULY 19, 1904.

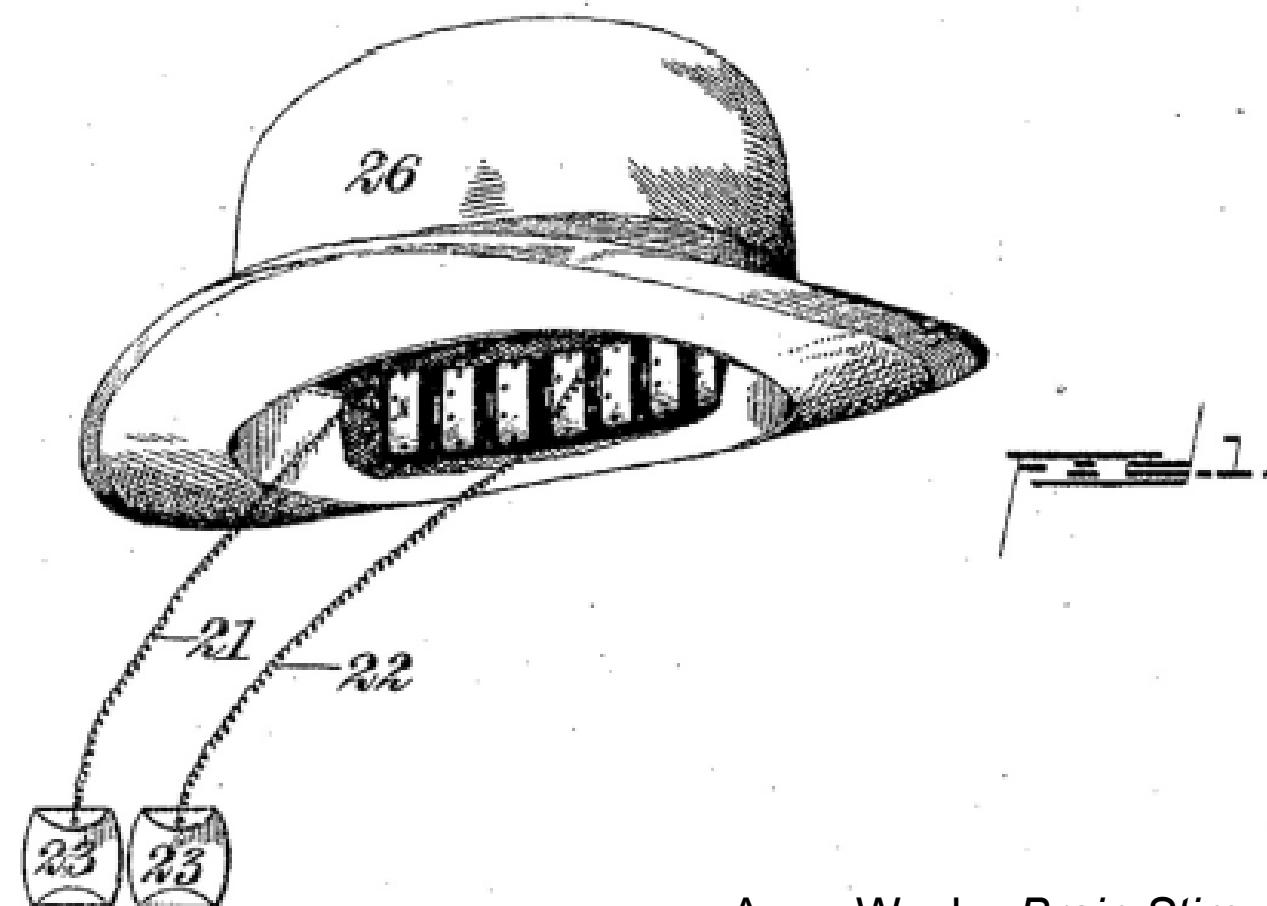
G. F. WEBB.

MEDICAL BATTERY.

APPLICATION FILED MAY 3, 1904.

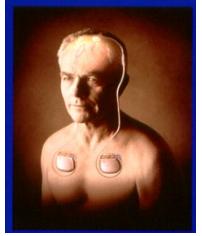
NO MODEL.

2 SHEETS—SHEET 1.



Brain Stimulation for Therapy

Invasive Brain Stimulation

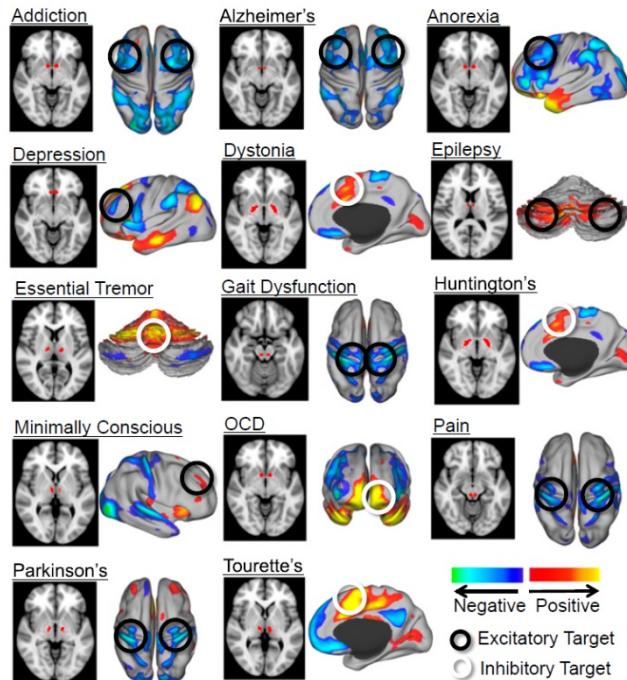


VNS

Vagus Nerve
Stimulation

DBS

Deep Brain
Stimulation



Convulsive Brain Stimulation

ECT

Electro-
convulsive
Therapy



MST

Magnetic
Seizure
Therapy



Non-invasive Transcranial Brain Stimulation (NTBS)



TMS

Transcranial Magnetic
Stimulation

tES

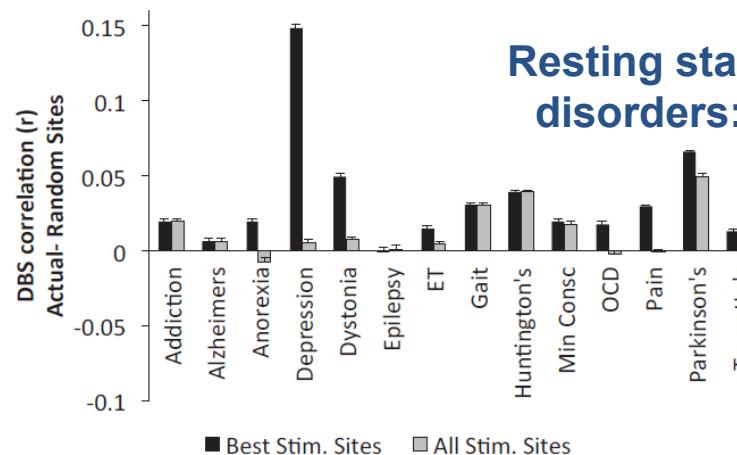
Transcranial Electrical Stimulation

Transcranial Direct Current Stimulation (tDCS),
Transcranial Alternating Current Stimulation (tACS)
Transcranial Random Noise Stimulation (tRNS)

tVNS

Transcutaneous Vagus Nerve
Stimulation

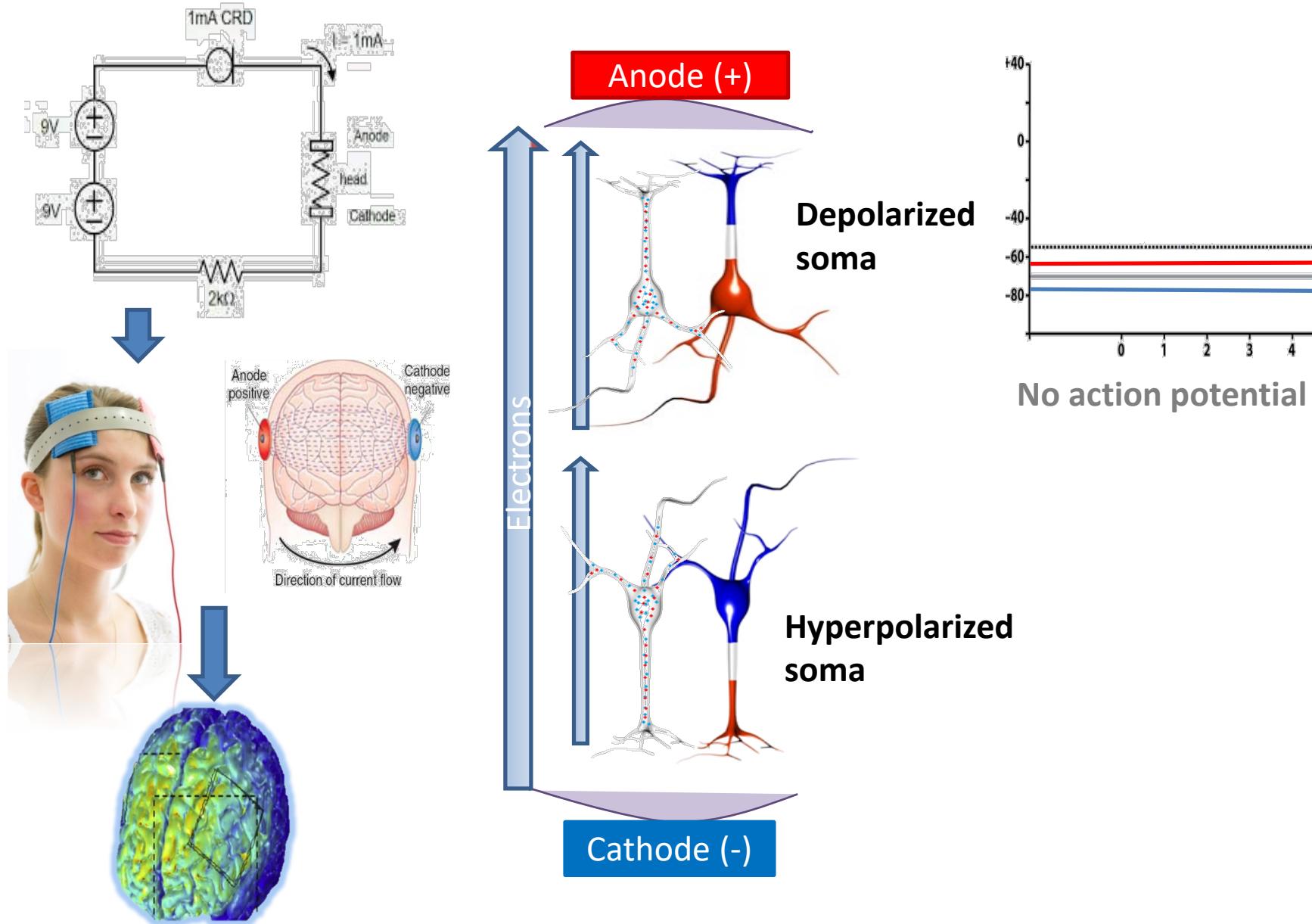
A Within Disease



Resting state fMRI connectivity across
disorders: DBS and NTBS converge

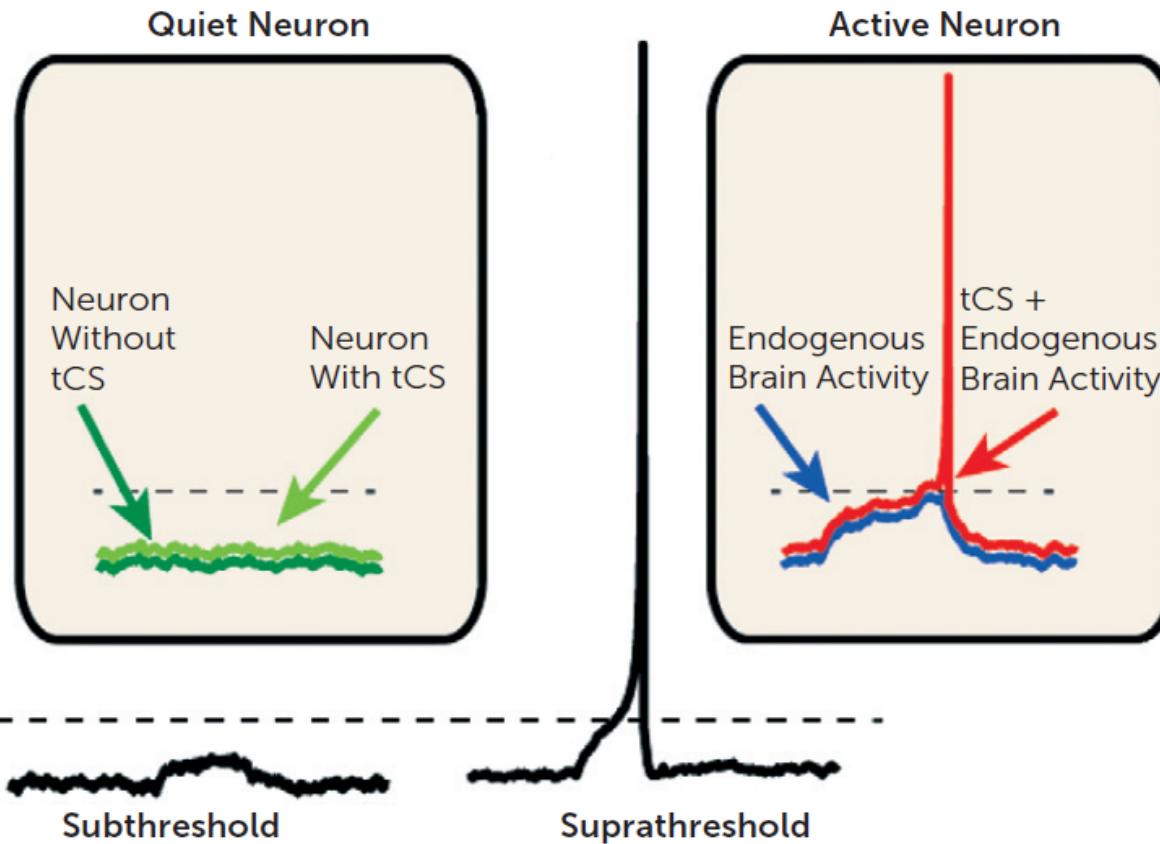
Fox et al. PNAS 2014

Transcranial Direct Current Stimulation (tDCS)



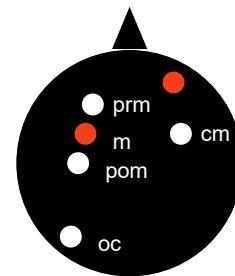
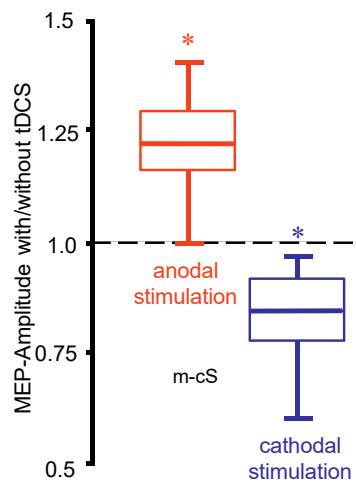
tDCS: Increasing endogenous and exogenous brain activity

FIGURE 1. Sub- and Suprathreshold Energy Input on Neuronal Action Potentials^a



^a Subthreshold membrane fluctuations are not sufficient to generate an action potential (left). However, if intrinsic fluctuations in a neuron's membrane voltage move it closer to its threshold, application of an inherently subthreshold input, such as low-intensity transcranial current stimulation (tCS), can trigger an action potential (right). Dashed line indicates threshold.

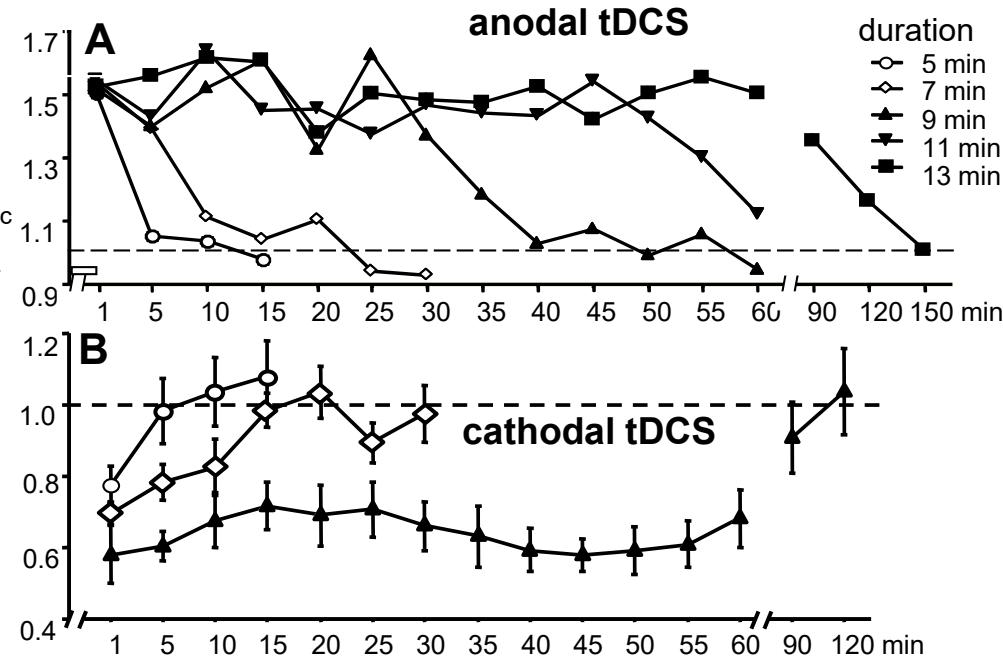
Polarity-dependent modulation of motor cortex excitability (MEP amplitudes) during and after tDCS



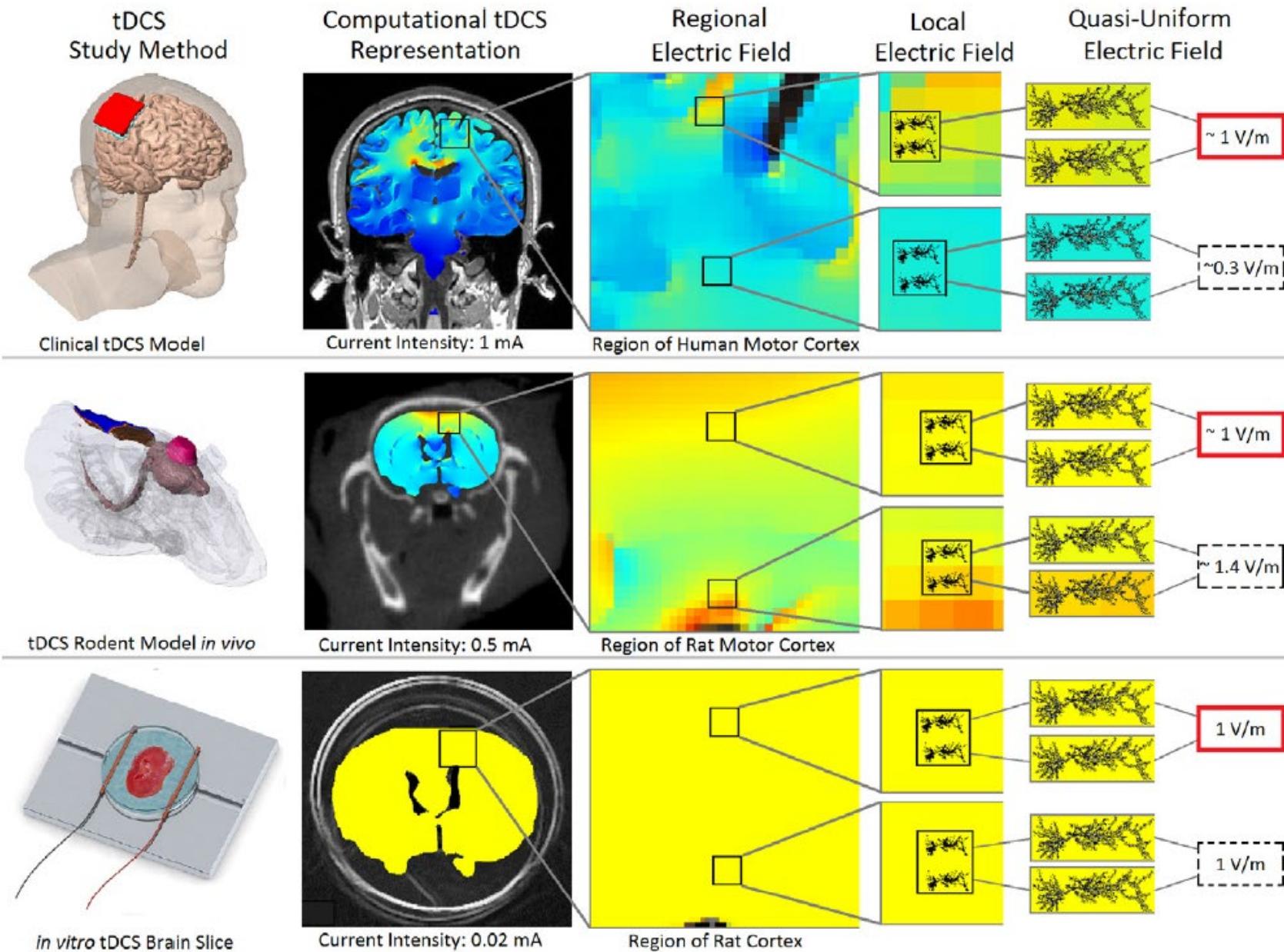
Electrode positions:
m = motor cortex; prm = premotor cortex;
pom = post-motor cortex; oc = occipital;
cS = contralateral forehead; cm = kontralateral motor cortex

Nitsche & Paulus 2000

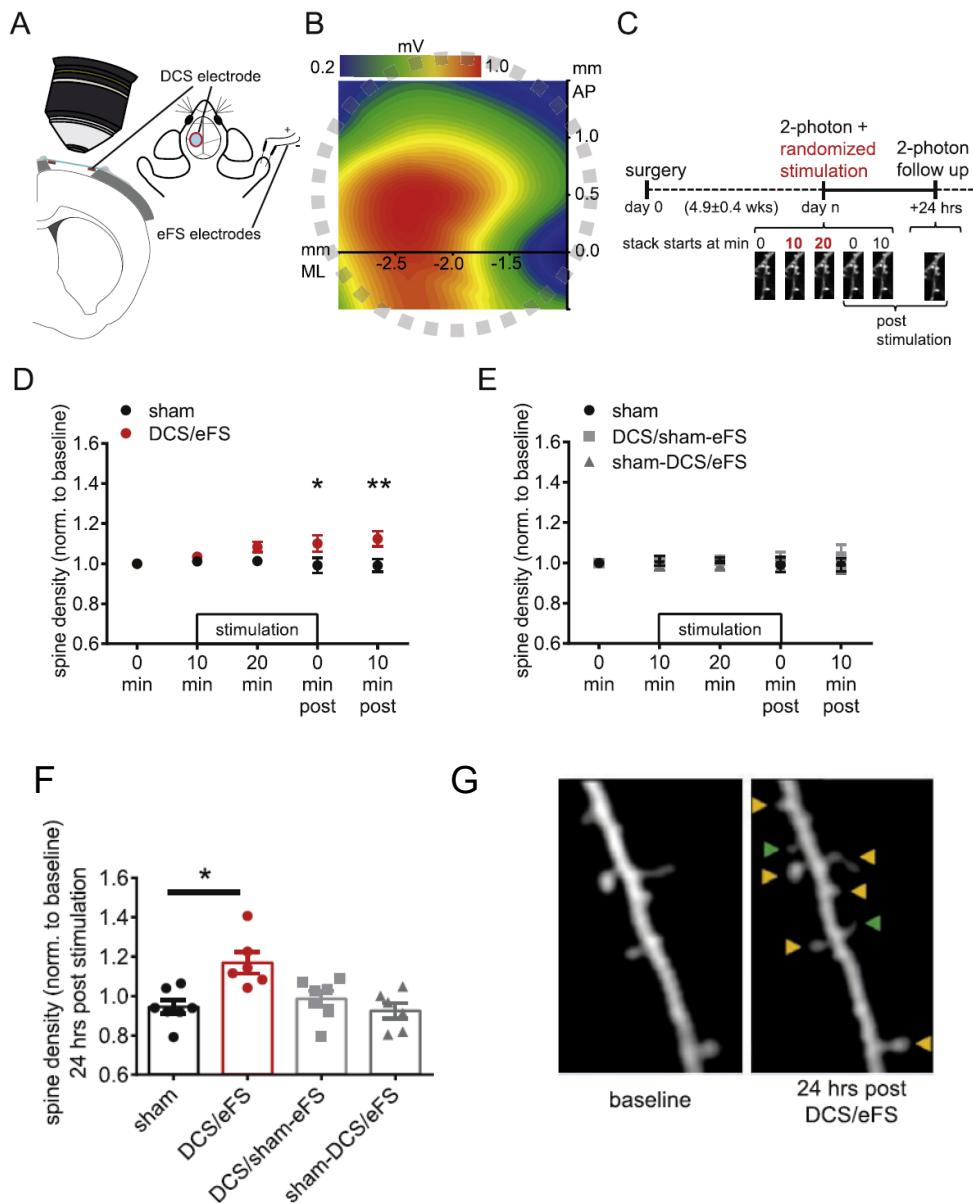
tDCS of the human motor cortex modulates MEP amplitudes depending on stimulation duration



Nitsche et al. *Clin Neurophysiol* 2003

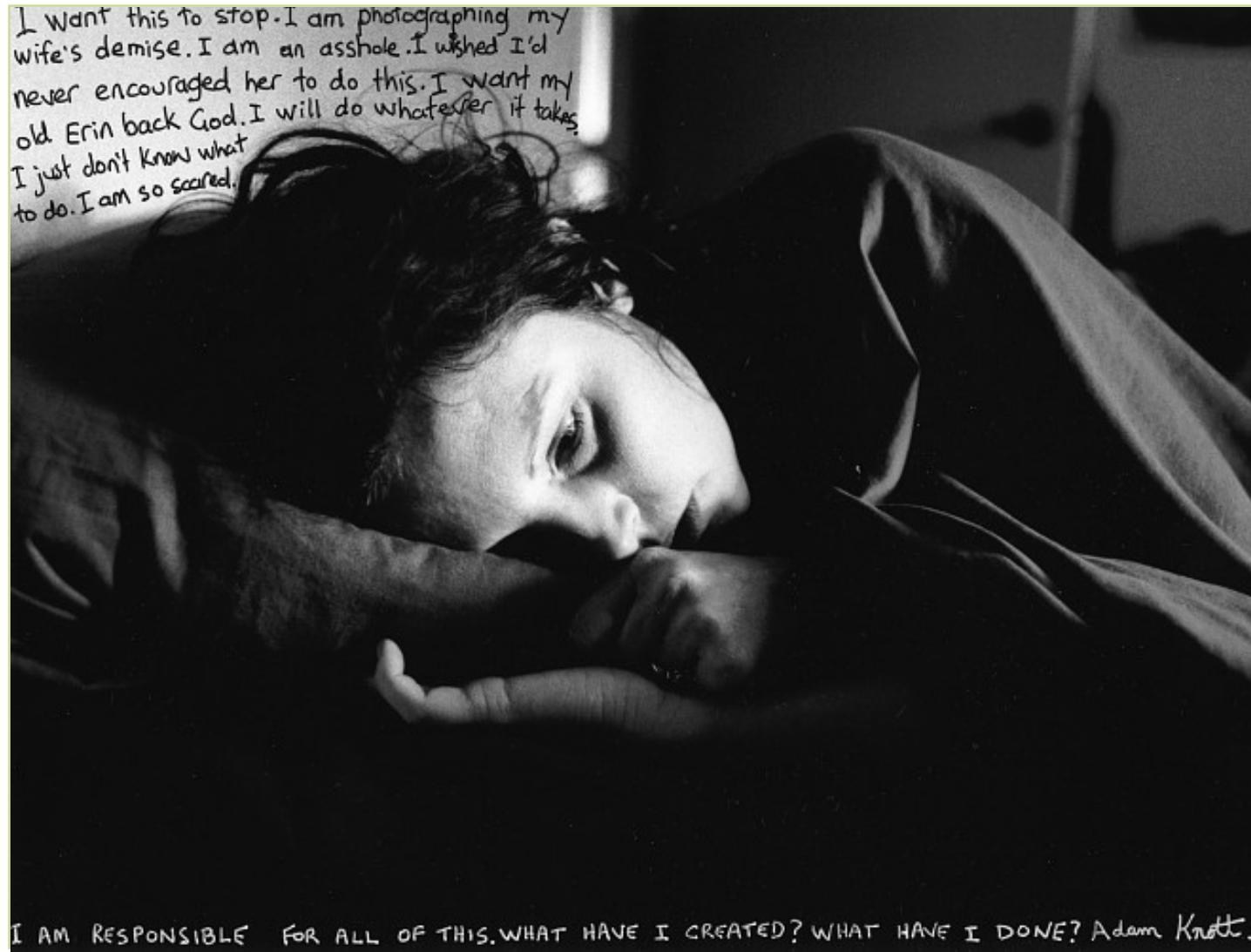


DCS-induced synaptic plasticity: structure follows function



- Anodal direct current stimulation (DCS) rapidly increased dendritic spine density in the sensorimotor cortex *in vivo* when combined with electrical forepaw stimulation (eFS).
- Changes outlasted the intervention for 24 h. This effect was due to increased survival of original spines and a preferential formation of new spines after intervention.
- The DCS-induced spine density increase was absent in mice with reduced BDNF expression.

Depressive Disorders

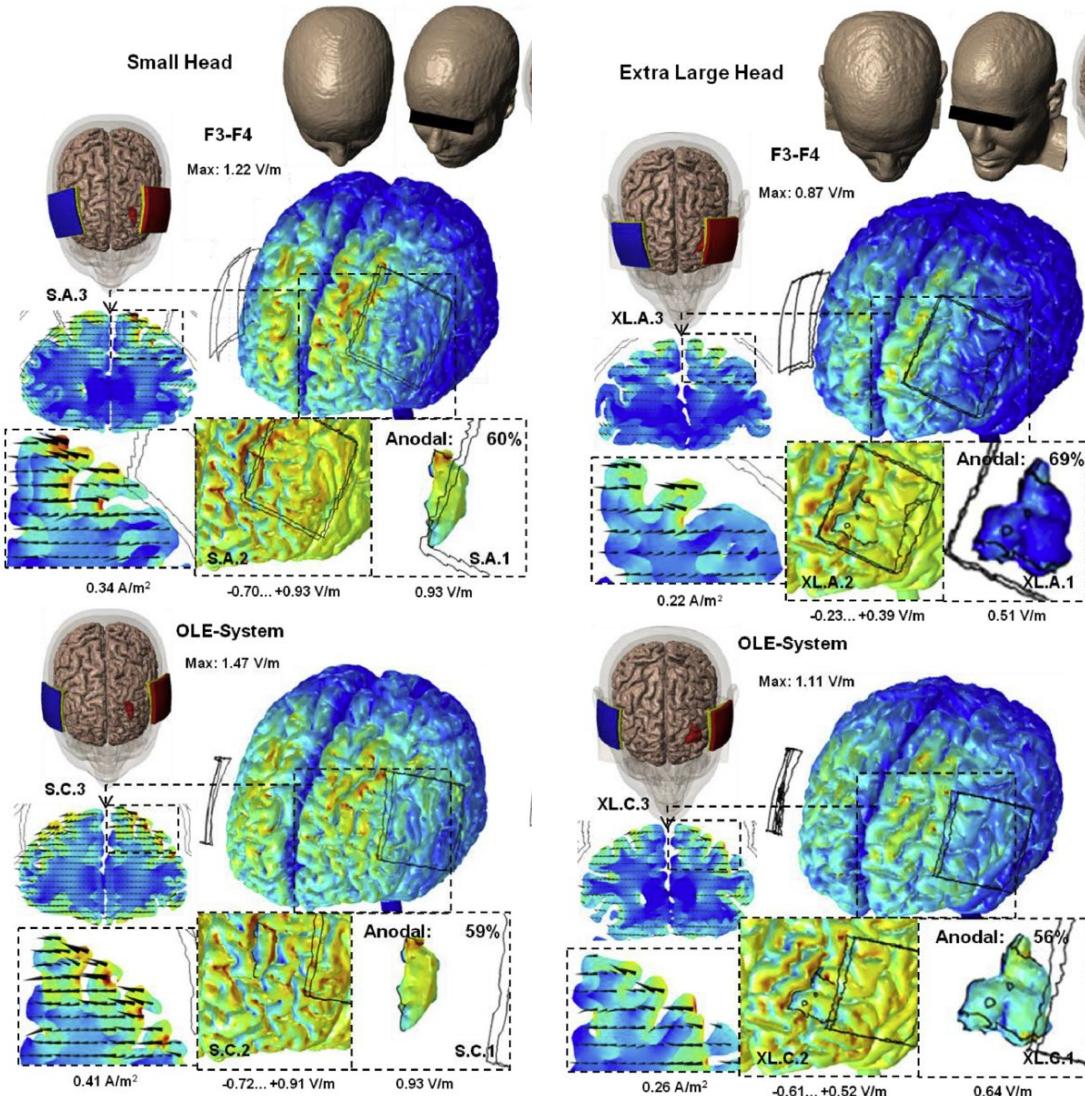


Computational electric field models and tDCS montage

GCBS



DLR Projektträger



- Mathematical models of electrical fields may guide electrode positioning.
- Stimulated regions vary with head size.
- Distance between electrodes may be critical.

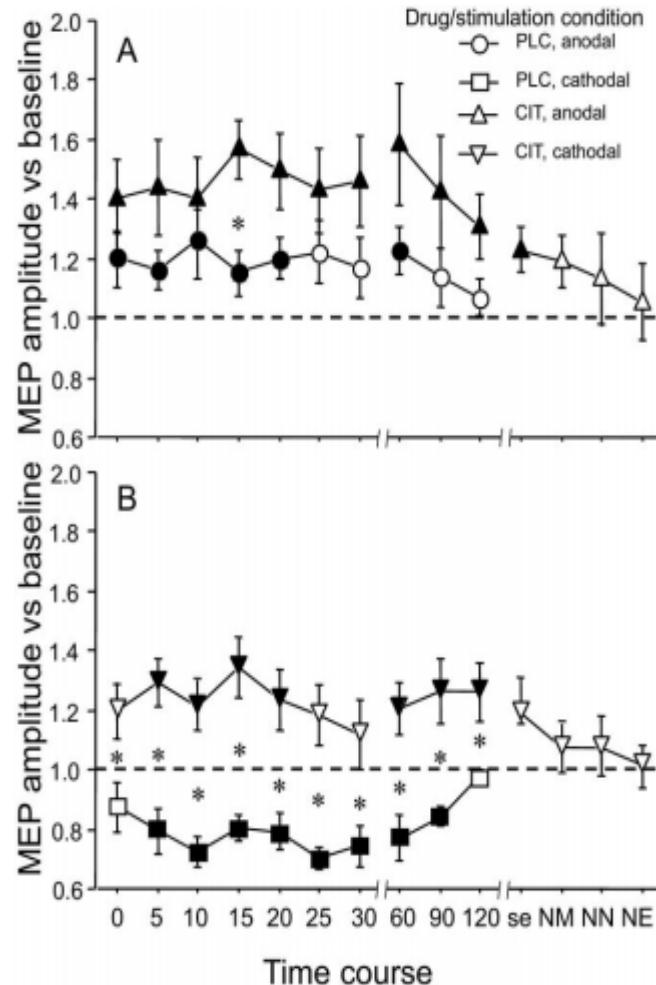
Trial 1: Antidepressant efficacy of combined tDCS/sertraline (*SELECT-tDCS trial, n=120*)

- **Patients**
 - 120 patients, 18-65 years
 - HDRS₁₇ > 17
 - No ADs at baseline
- **Primary aim**
 - To assess the combined efficacy of tDCS + AD compared to tDCS, AD or placebo.
- **Interventions**
 - Sertraline 50mg/day.
 - 12 tDCS sessions (2-mA, 30-min).

Factorial design

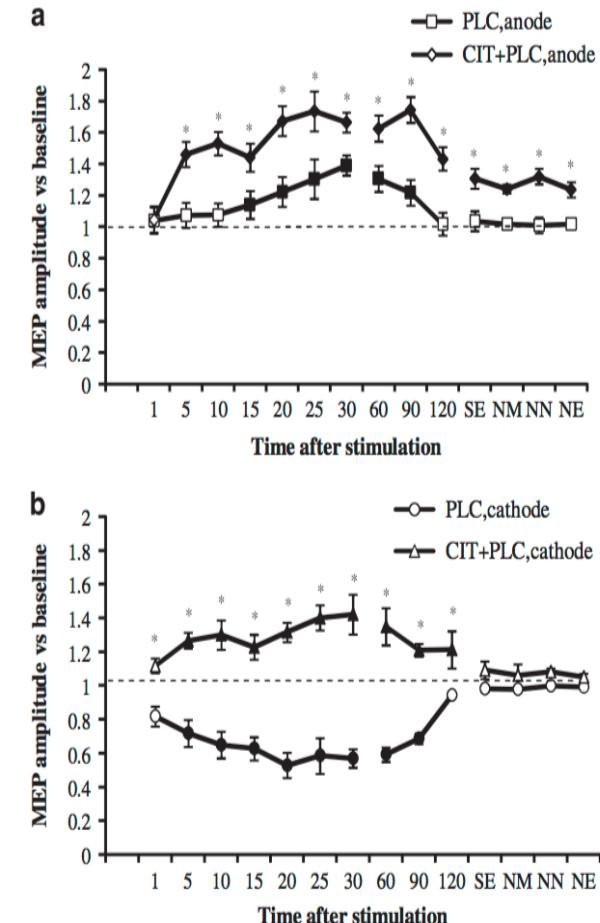
Sham tDCS/ Placebo	Sham tDCS /Sertraline
Active tDCS /Placebo	Active tDCS/ Sertraline

tDCS plasticity enhanced by SSRI



Single citalopram dose

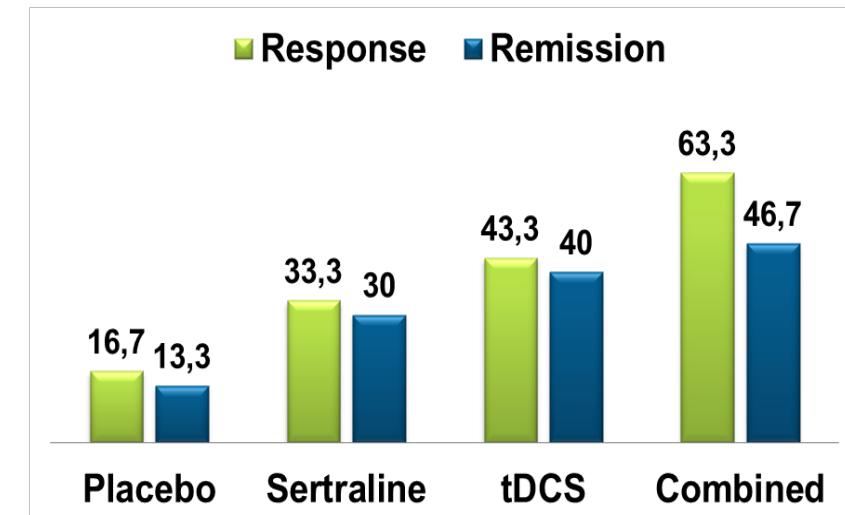
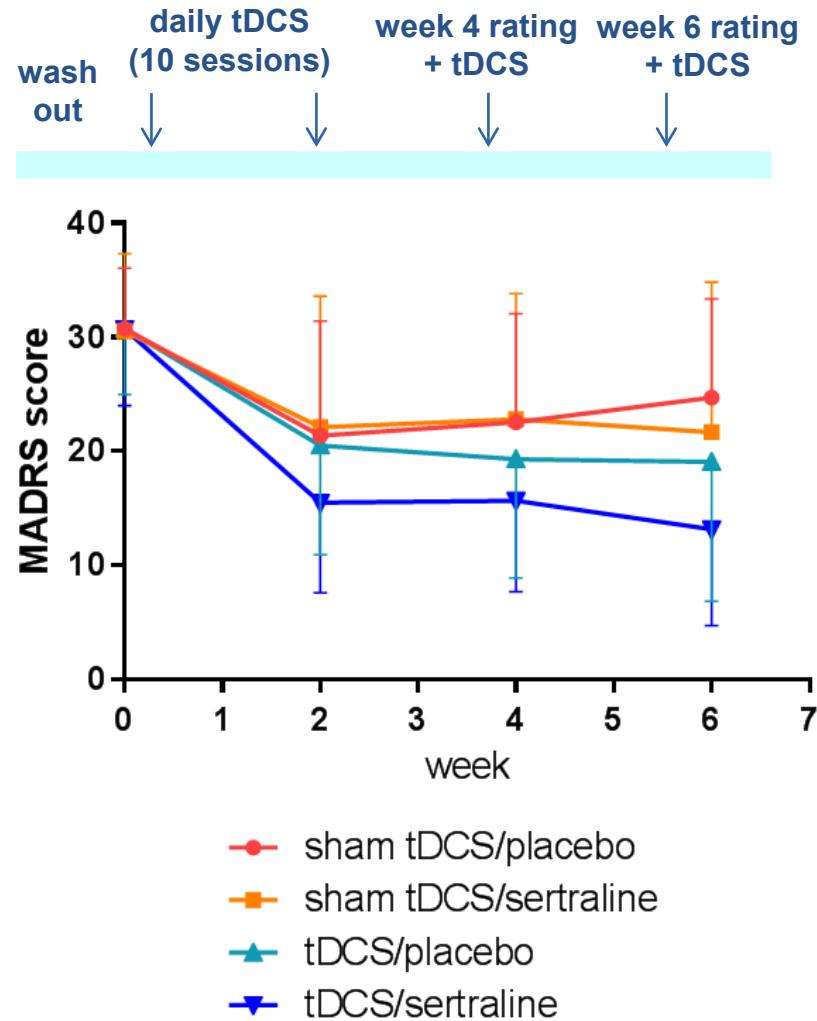
Nitsche et al., 2009



Chronic (>2weeks) of citalopram

Kuo et al., 2016

Antidepressant efficacy of combined tDCS/sertraline (*SELECT-tDCS trial, n=120*)



Trial 2: The Escitalopram versus Electric Current Therapy for Treating Depression Clinical Study (ELECT-tDCS): a non-inferiority, triple-arm, placebo-controlled clinical trial

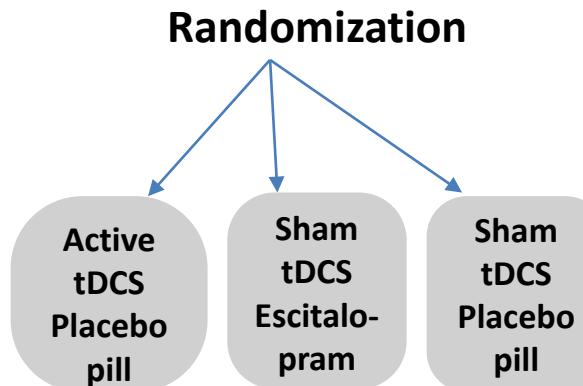
- **Patients:** 245 patients, 18-75 years

HDRS > 17, no AD at baseline

- **Interventions:** Escitalopram 20mg/day for 10 weeks,

22 tDCS sessions (2 mA, 30-min): 3 weeks consecutively, then once a week until week 10.

Omni-Lateral-Electrode (OLE) positioning (Soterix)

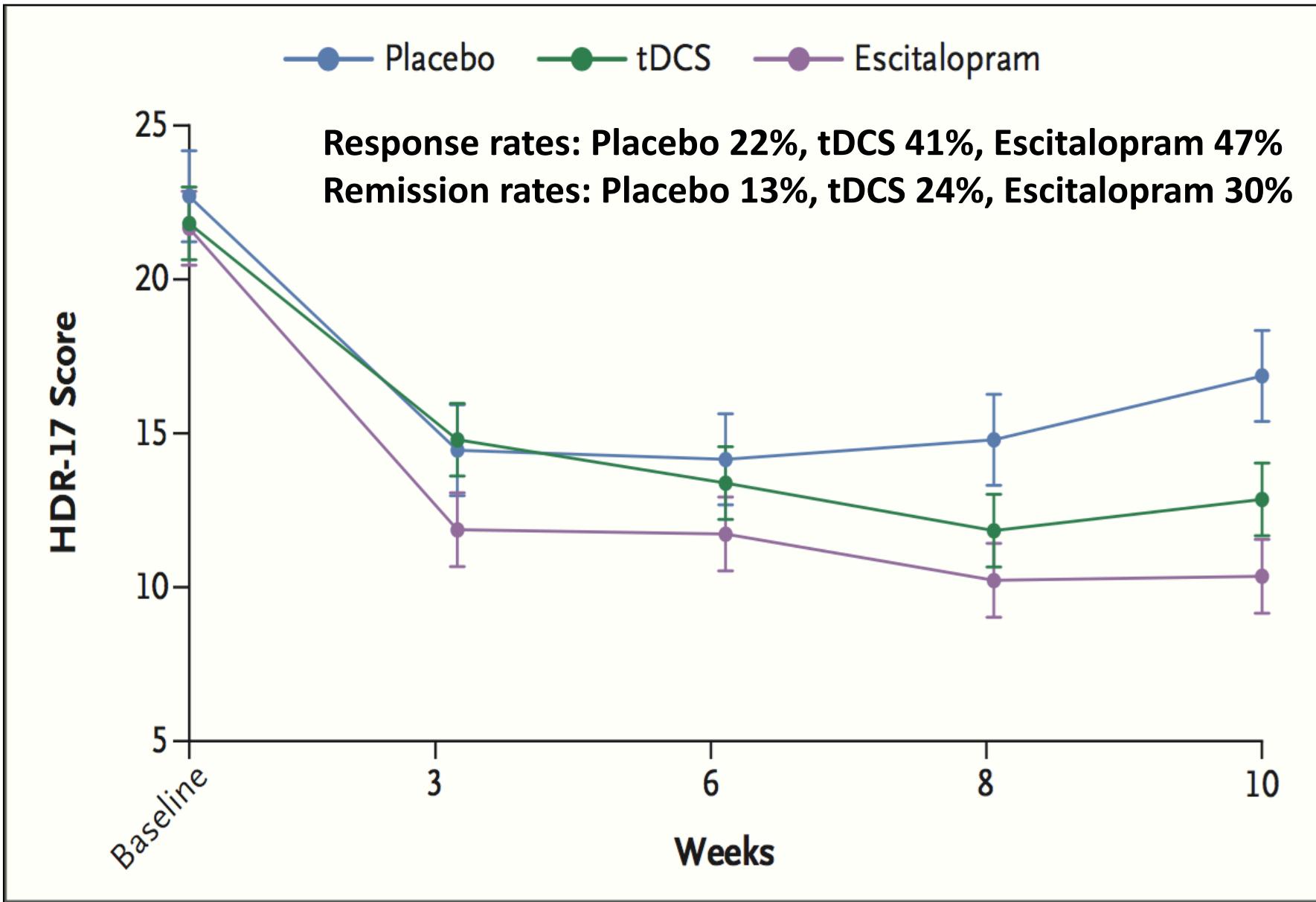


Non-inferiority design with placebo

Table 1. Demographic and Clinical Characteristics of the Patients at Baseline.*

Characteristic	Placebo (N=60)	Escitalopram (N=91)	tDCS (N=94)
Female sex — no. (%)	41 (68)	61 (67)	64 (68)
Age — yr			
Current	40.9±12.9	41.8±12.5	44.6±11.8
At onset of depression	25.7±11.3	26.4±12.0	26.4±11.7
Type of depression — no. (%)			
Recurrent	44 (73)	59 (65)	59 (63)
Chronic	29 (48)	46 (51)	42 (45)
Severe	22 (37)	25 (27)	28 (30)
Melancholic	22 (37)	37 (41)	34 (36)
Atypical	18 (30)	25 (27)	30 (32)
Any anxiety disorder — no. (%)†	38 (63)	46 (51)	56 (60)
Family history of psychiatric disorder — no. (%)	39 (65)	57 (63)	64 (68)
History of treatment for depression			
No. of treatment failures			
In current episode	1.0±1.4	0.9±1.5	1.0±1.2
Over lifetime	4.9±4.3	4.5±3.9	4.8±3.8
Treatment resistance — no. (%)	19 (32)	25 (27)	30 (32)
Current use of benzodiazepines — no. (%)	17 (28)	20 (22)	31 (33)
HDRS-17 score‡§	22.7±4.3	21.7±3.5	21.8±3.9
MADRS score¶	28.1±6.8	26.2±6.0	27.4±7.0
Beck Depression Inventory score	31.1±11.1	29.4±8.8	30.9±9.2

ELECT-TDCS: Main outcome



Trial 3: Australian-US trial: A Controlled Trial of tDCS as a Treatment for Unipolar and Bipolar Depression

N=120 (6 sites), 2 arms (active tDCS, sham tDCS)

ClinicalTrials.gov: NCT01562184

Major depressive episode (DSM-IV) with duration of at least 4 weeks

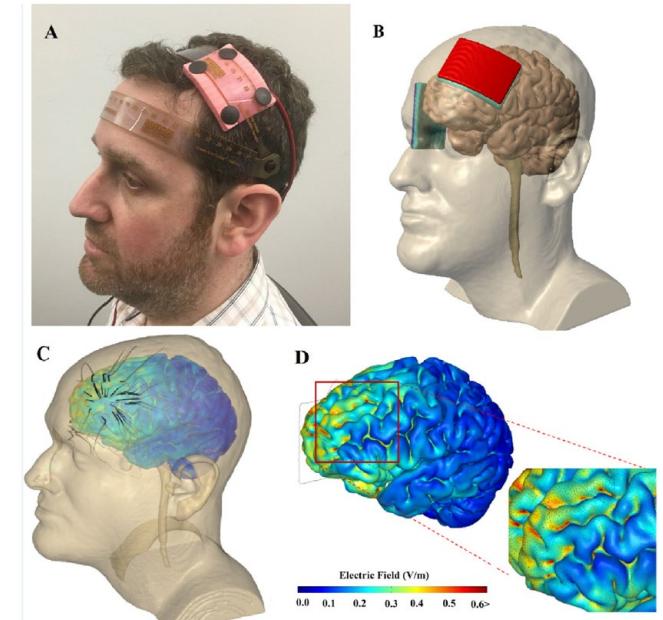
4 weeks sham controlled, 4 weeks open label (active), 2 weeks taper phase,
2.5 mA, 30 min, anode F3, cathode F8

Sham: ramp up 1 mA 10s, ramp down 1 min, further ramp up/down to 0.5 mA at 10 und 20 min,
constant current 0.034 mA

Primary outcome: MADRS

Table 1
Baseline demographic and clinical characteristics.

	Unipolar	Bipolar	Range
n	84	36	—
Gender (m/f)	42/42	15/21	—
tDCS condition	Sham	Active	—
n	42	42	—
Age (m, SD)	46.74 (16.30)	48.93 (12.34)	—
Duration of current MDE in months (m, SD)	12.42 (10.40)	12.30 (8.17)	1–36
Total lifetime duration of MDE in months (m, SD)	124.42 (129.28)	153.31 (128.04)	4–624
Number of previous MDE (m, SD)	8.40 (10.68)	12.64 (14.97)	0–123
Number of antidep failed in current MDE (m, SD)	1.10 (0.93)	1.29 (0.94)	0–3
Total lifetime failed antidep (m, SD)	4.31 (2.91)	4.30 (3.46)	0–16
Maudsley Total (m, SD)	5.90 (1.56)	5.95 (1.23)	4–10
<i>Concurrent medications:</i>			
Benzodiazepine (Y)	7	6	—
Antidepressant (Y)	29	27	—
Antipsychotic (Y)	5	4	—
Lithium (Y)	2	2	—
Mood stabiliser/anticonvulsant (Y)	2	5	—
BDNF genotype (Val/Val/Met)	22/13	21/8	—
	10/3	10/7	—

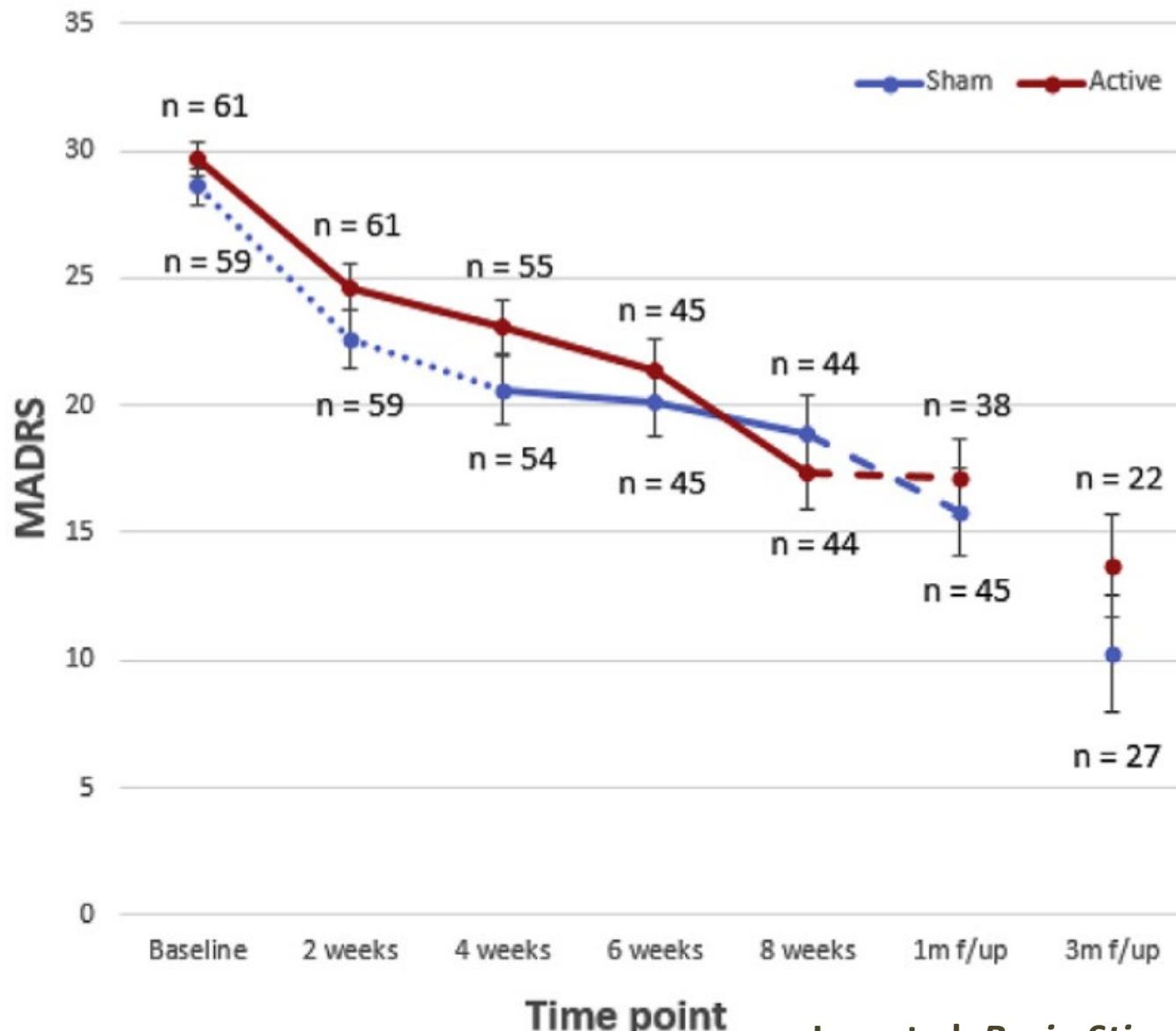


Alonso et al. *Contemporary Clinical Trials* 2016

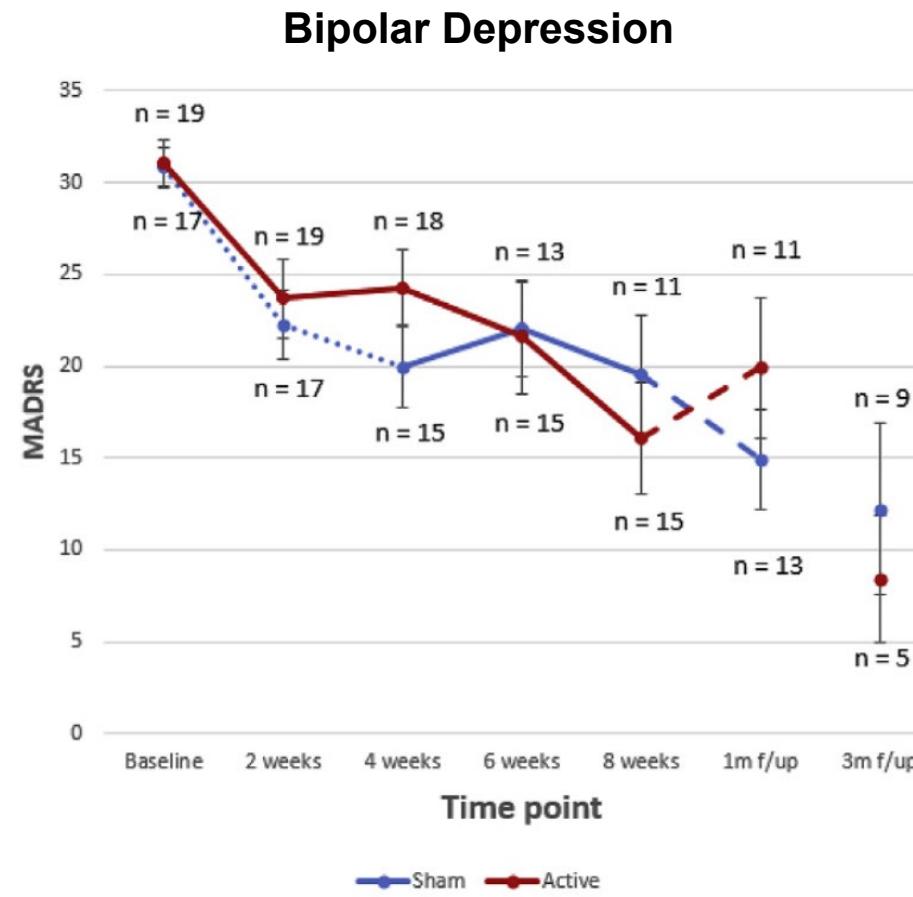
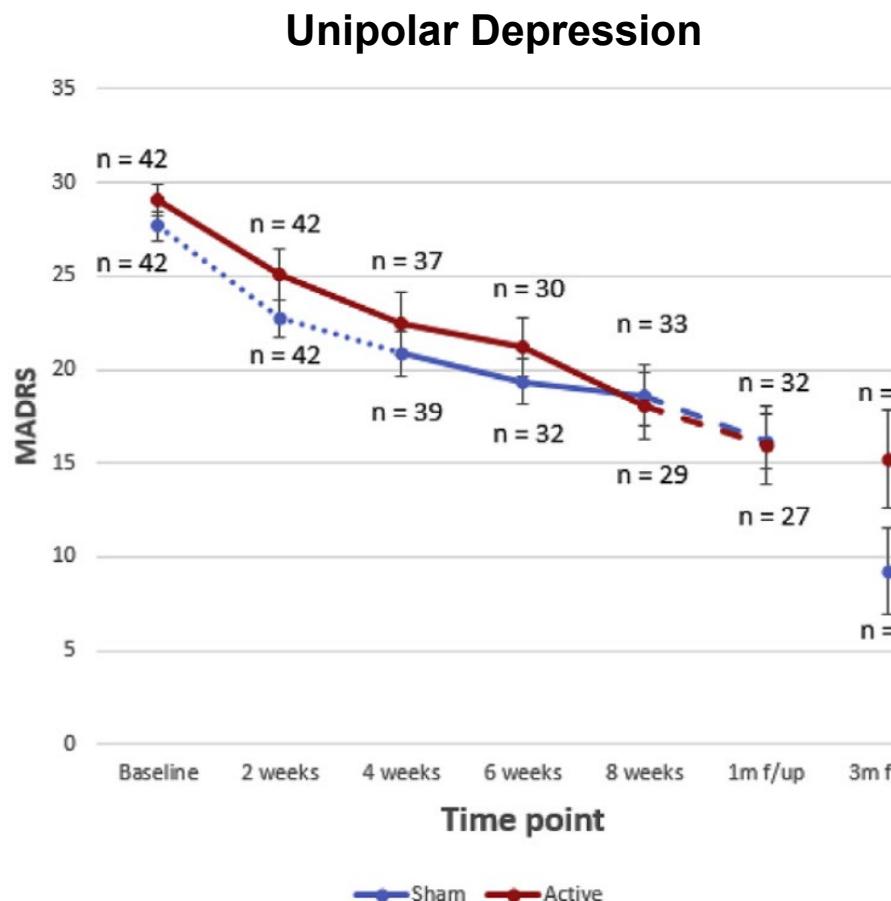
Loo et al. *Brain Stimulation* 2018

Australian U.S. RCT of tDCS in depression

Primary outcome: change in MADRS score (4 weeks)



Australian U.S. RCT of tDCS in depression unipolar vs bipolar depression



Australian U.S. RCT of tDCS in depression

Adverse effects

Table 2

Adverse effects and incidence (n = number of sessions in which adverse effect reported; % = number sessions in which adverse effect reported against the total number of sham or active sessions in study phase as applicable).

	Randomized-controlled phase				Open label phase	
	Sham (Total number of sessions = 1104)		Active (Total number of sessions = 1127)		Active (Total number of sessions = 1704)	
	n	%	n	%	n	%
Blurred Vision	5	0.5	34	3.0	2	0.1
Burning	197	17.8	409	36.3	653	38.3
Fatigue	41	3.7	74	6.6	75	4.4
Headache	39	3.5	102	9.1	68	4.0
Itching	122	11.1	262	23.2	287	16.8
Light-headedness/Dizziness	19	1.7	133	11.8	51	3.0
Nausea	1	0.1	27	2.4	18	1.1
Pain	10	0.91	24	2.1	22	1.3
Redness	289	26.2	566	50.2	942	55.3
Tingling	456	41.3	588	52.2	928	54.5
Other	94	8.5	108	9.6	119	7.0



Safety and Application Guidelines

Low intensity transcranial electrical stimulation (TES) in humans, encompassing transcranial direct current (tDCS), transcutaneous spinal Direct Current Stimulation (tsDCS), transcranial alternating current (tACS), and transcranial random noise (tRNS) stimulation or their combinations, appears to be safe. No serious adverse events (SAEs) have been reported so far in over 18,000 sessions administered to healthy subjects, neurological and psychiatric patients, as summarized here. Moderate adverse events (AEs), as defined by the necessity to intervene, are rare, and include skin burns with tDCS due to suboptimal electrode-skin contact. Very rarely mania or hypomania was induced in patients with depression (11 documented cases), yet a causal relationship is difficult to prove because of the low incidence rate and limited numbers of subjects in controlled trials. Mild AEs (MAEs) include headache and fatigue following stimulation as well as prickling and burning sensations occurring during tDCS at peak-to-baseline intensities of 1–2 mA and during tACS at higher peak-to-peak intensities above 2 mA.

Safety is established for low-intensity ‘conventional’ TES defined as <4 mA, up to 60 min duration per day. Animal studies and modeling evidence indicate that brain injury could occur at predicted current densities in the brain of 6.3–13 A/m² that are over an order of magnitude above those produced by tDCS in humans. Using AC stimulation fewer AEs were reported compared to DC. In specific paradigms with amplitudes of up to 10 mA, frequencies in the kHz range appear to be safe.

Guidelines

Low intensity transcranial electric stimulation: Safety, ethical, legal regulatory and application guidelines

A. Antal ^{a,*}, I. Alekseichuk ^a, M. Bikson ^b, J. Brockmöller ^c, A.R. Brunoni ^d, R. Chen ^e, L.G. Cohen ^f, G. Dowthwaite ^g, J. Ellrich ^{h,i,j}, A. Flöel ^k, F. Fregni ^l, M.S. George ^m, R. Hamilton ⁿ, J. Haueisen ^o, C.S. Herrmann ^p, F.C. Hummel ^{q,r}, J.P. Lefaucheur ^s, D. Liebetanz ^t, C.K. Loo ^t, C.D. McCaig ^u, C. Miniussi ^{v,w}, P.C. Miranda ^x, V. Moliadze ^y, M.A. Nitsche ^{z,a,o}, R. Nowak ^{ab}, F. Padberg ^{ac}, A. Pascual-Leone ^{ad}, W. Poppendieck ^{ae}, A. Priori ^{af}, S. Rossi ^{ag}, P.M. Rossini ^{ah}, J. Rothwell ^{ai}, M.A. Rueger ^{aj}, G. Ruffini ^{ab}, K. Schellhorn ^{ak}, H.R. Siebner ^{al,am}, Y. Ugawa ^{an,ao}, A. Wexler ^{ap}, U. Ziemann ^{aq}, M. Hallett ^{ar,l}, W. Paulus ^{a,t}

Aktuelle Entwicklungen und Perspektiven

Personalized therapy instead of “one size fits all” approach?

The person and
the disease



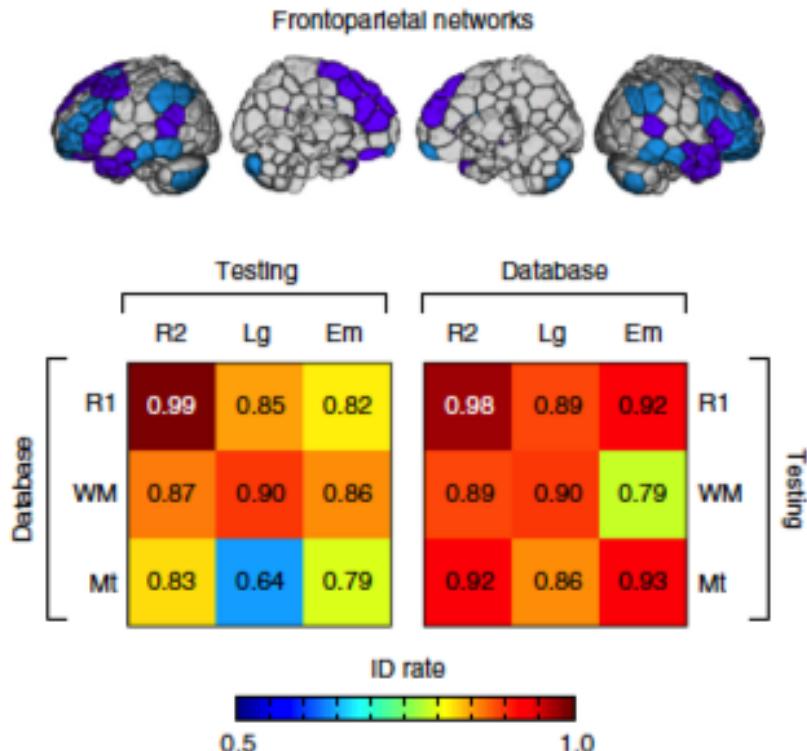
The intervention

NTBS: „Dosage at Target“

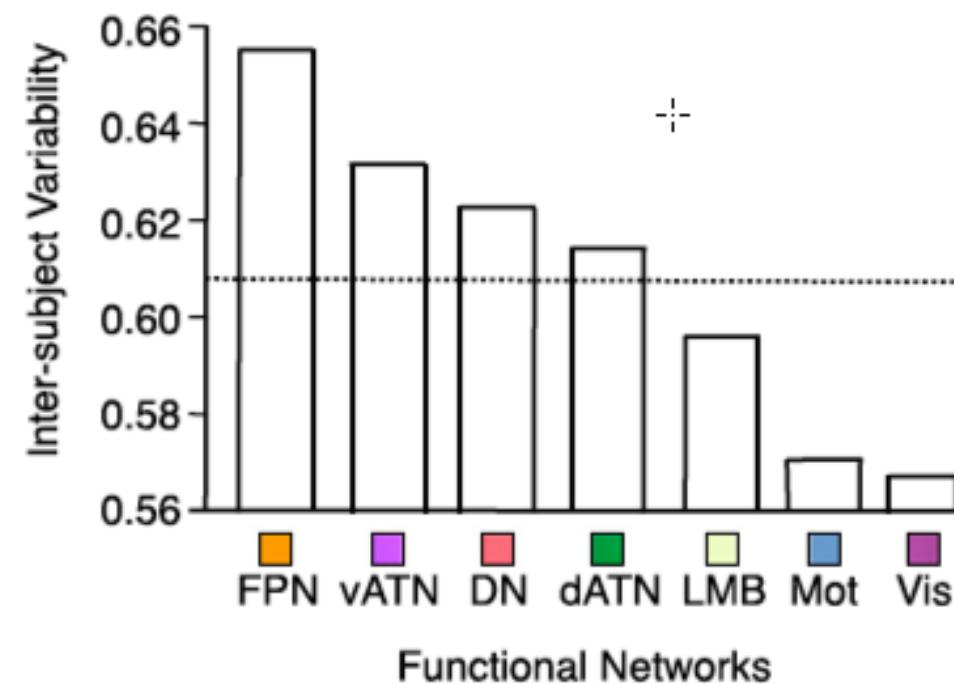
- Technical parameters and their interaction with targets: Sites, circuits, cells, states, dynamics
- Combining NTBS and training or psychotherapy?

Gene x Environment
State x Trait (system level)

Intersubject variability of resting state functional connectivity



Finn et al, Nature Neuroscience 2015



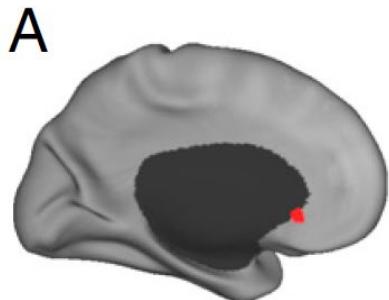
Mueller et al., Neuron 2013



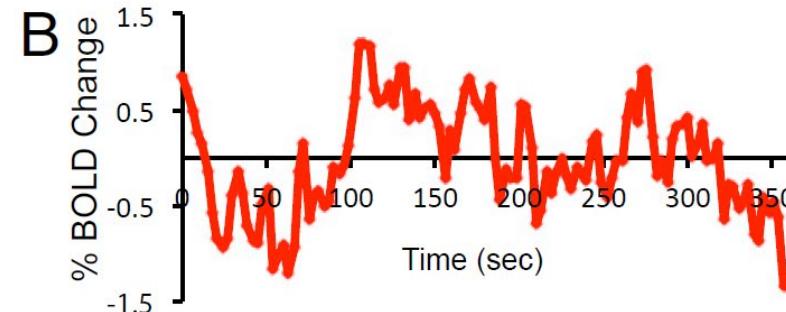
Sophia Stöcklein
née Müller

Resting state fMRI connectivity: Cg25 (DBS) and left DLPFC (rTMS)

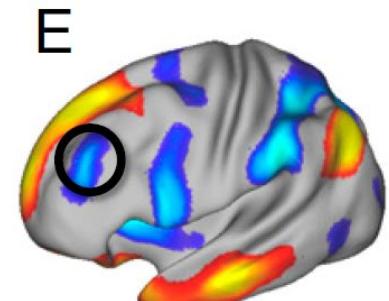
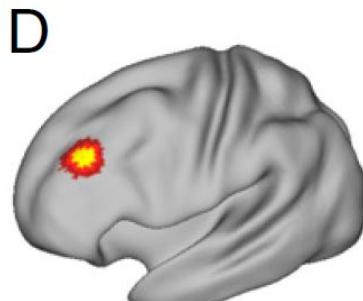
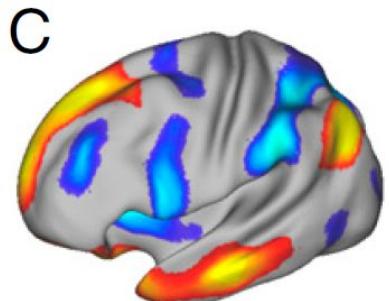
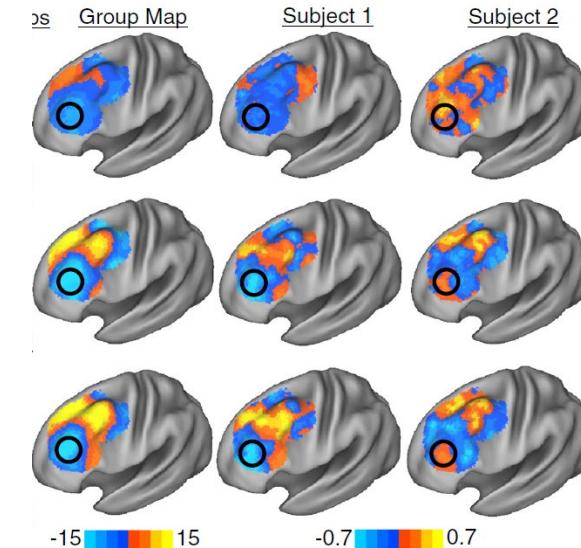
DBS ROI (Cg25)



rsfMRI signal for DBS ROI (N=1.000)



Interindividual
Variation



whole brain DBS
correlation map

NIBS ROI (left DLPFC)

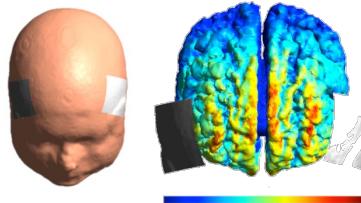
Fox et al. PNAS 2014

Fox et al. Neuroimage 2013

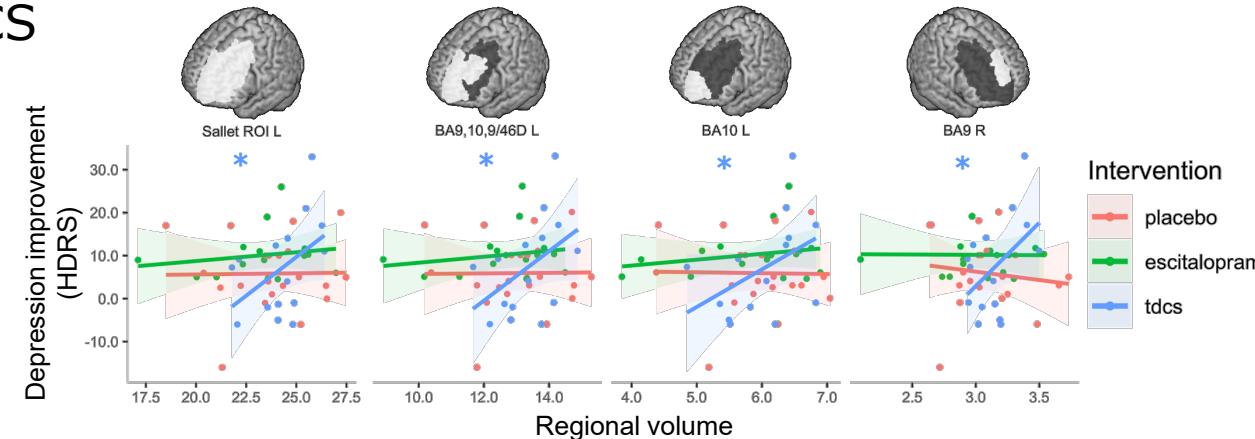


Project (1) - Results

- Baseline volume of PFC is associated with improvement of depression after tDCS



Bulubas et al. 2019; Brain Stim
12(5):1197-204



- No association of functional connectivity of structurally based regions and depression improvement

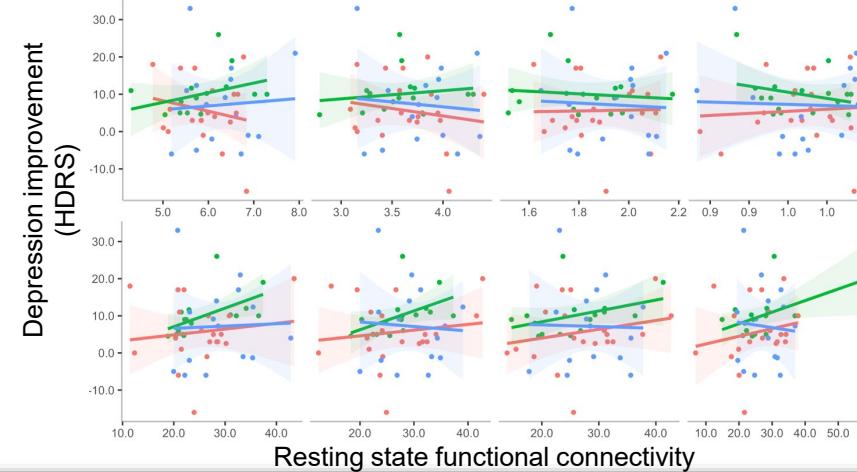


Lucia Bulubas, Daniel Keeser

➤ Locally

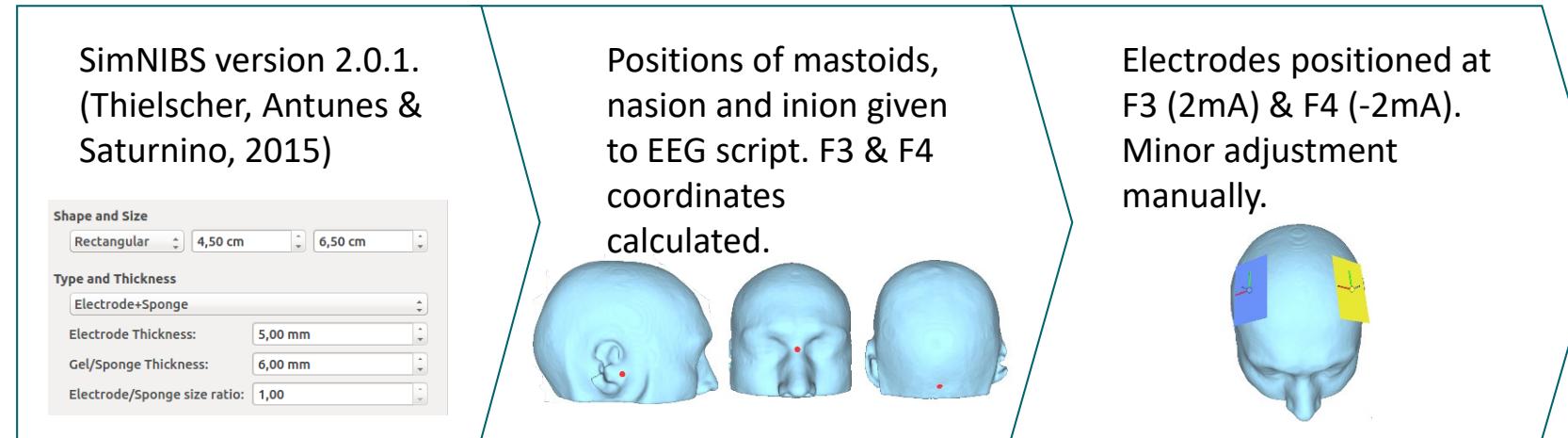
➤ Globally

Bulubas et al. 2021 Eur Arch Psychiatry
Clin Neurosci. 271(1):123-134





Transdiagnostic comparison in a computational model of tDCS induced efields using SimNIBS



T1 w structural MRI images
(Magnetom Skyra, 3T)

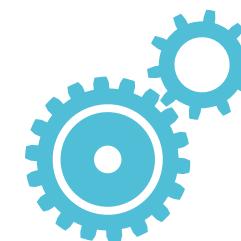
Diagnostic groups:

24 Scz

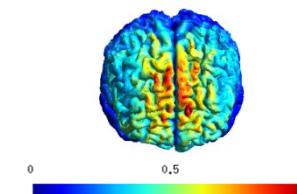


25 MDD

25 HC



E-fields at 50, 75, 90, 95, 99 and 99.5 percentiles



Scans loaded onto SimNIBS

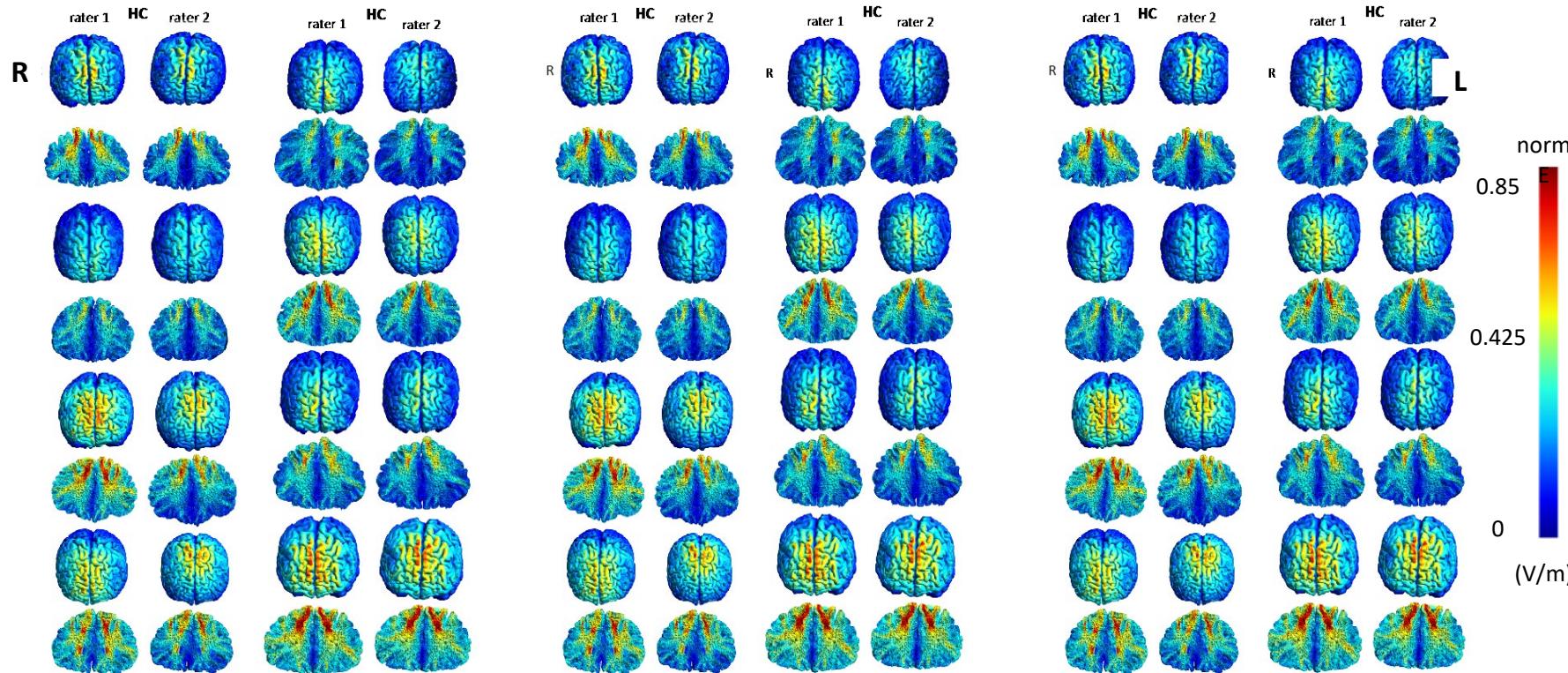
- Investigator 1: S.H., investigator 2: Y.M.
- Blinded for diagnostic groups



Yuki Mizutani, Shun Takahashi et al. in preparation

Transdiagnostic comparison in a computational model of tDCS induced efields using SimNIBS

Inter-individual difference (native space)



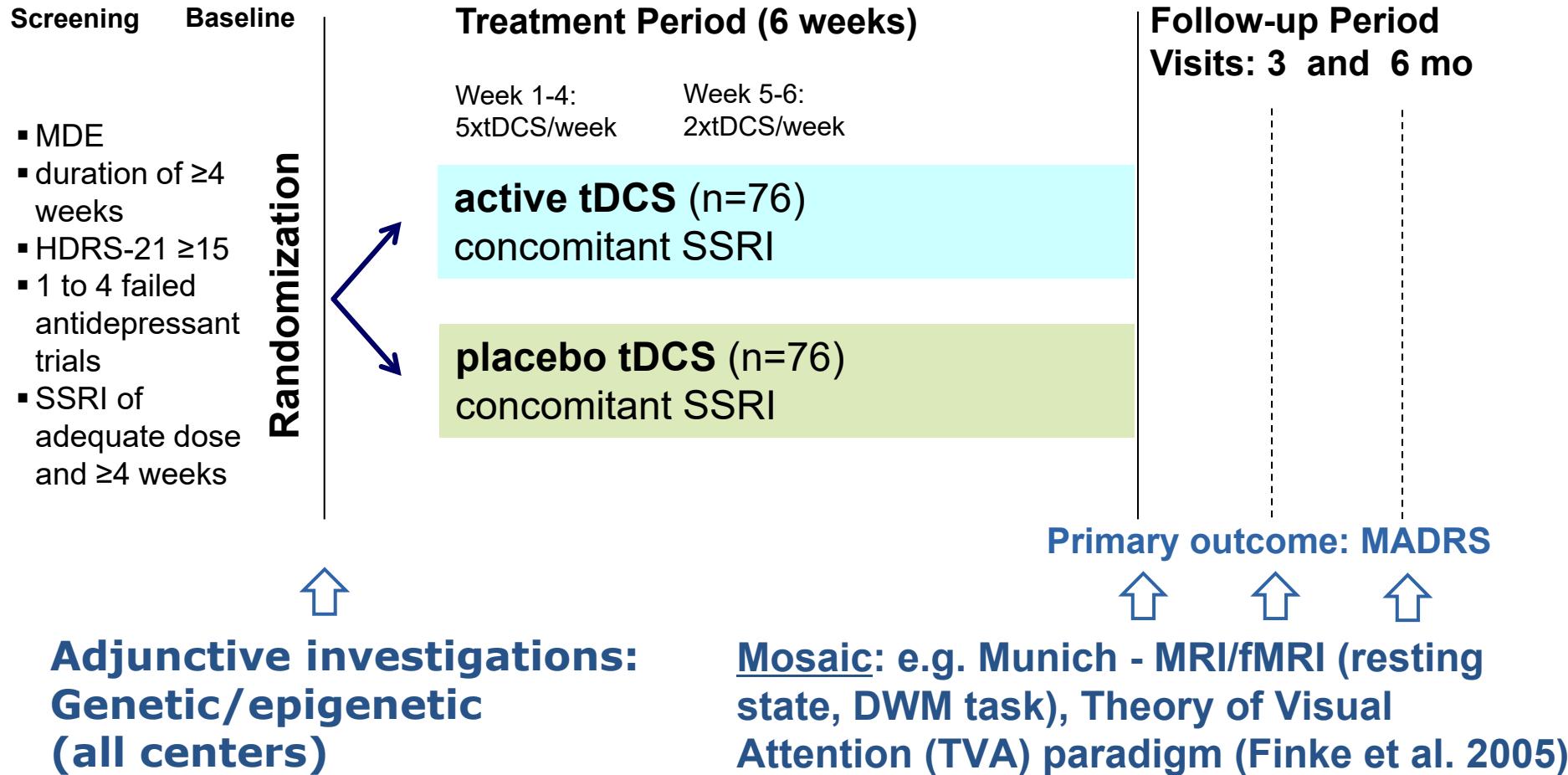
- Inter-individual difference is big within subject groups
- Stimulation of Rater 1 is more anterior and the e-field tends to be stronger



GCBS-WP7: The DepressionDC Trial



tDCS as Treatment for Major Depression – A Prospective Multicenter Double Blind Randomized Placebo Controlled Trial





Munich November 2012: 1st tDCS group therapy for enhancing psychotherapy in smoking cessation



WP6: PsychotherapyPlus Study



GCBS



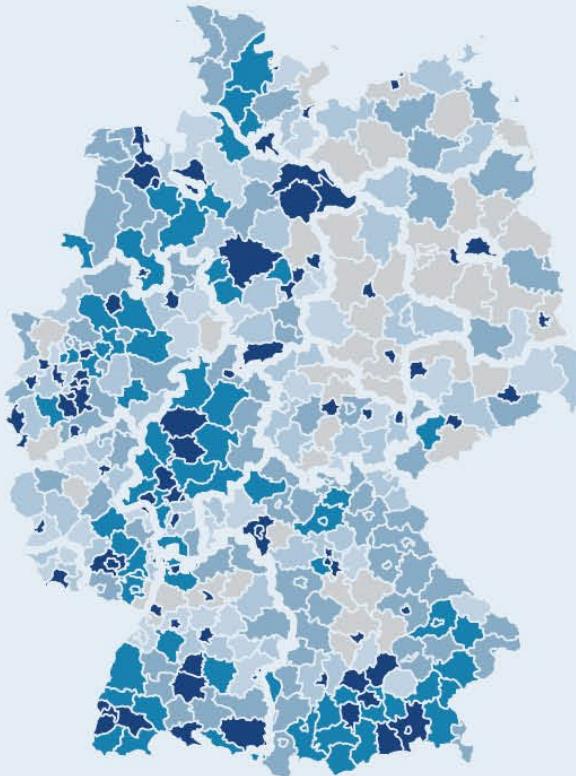
M. Bajbouj, S. Aust
Charité Berlin



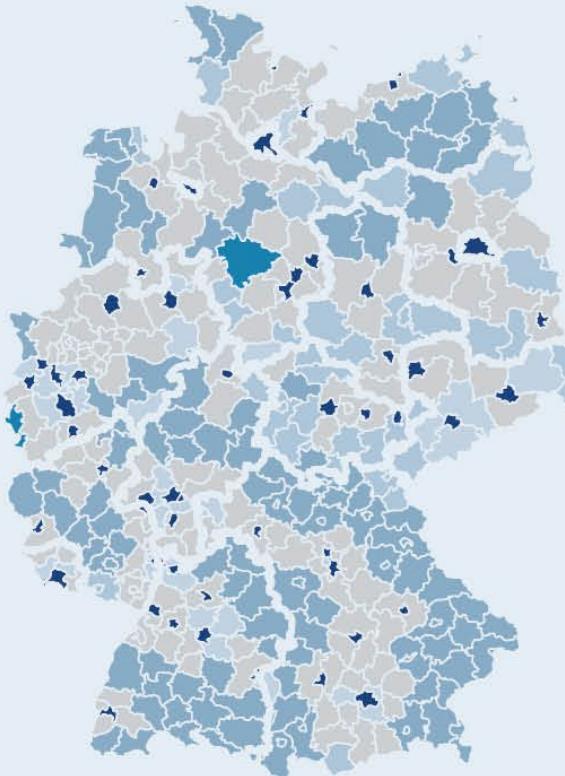
Low Tech NTBS als Home Treatment?

Anzahl Psychotherapeuten je 100.000 Einwohner, 2015 (Plankreise)

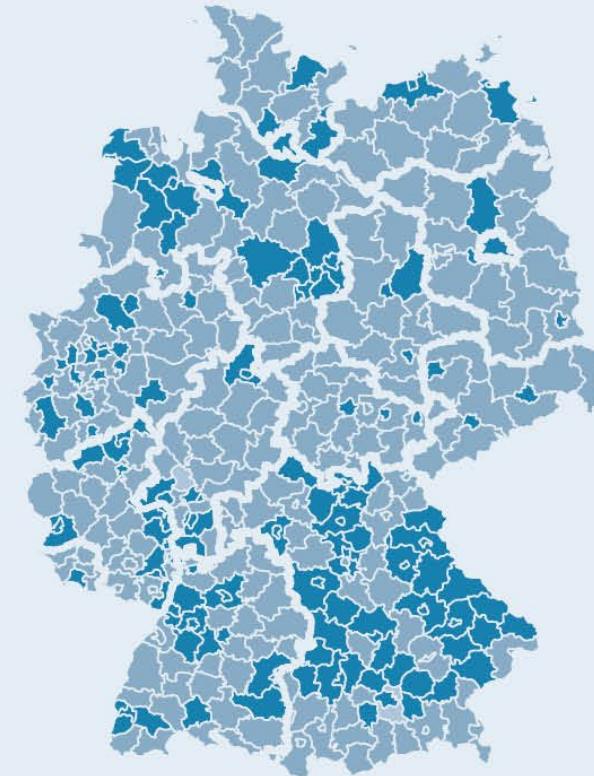
Status quo



Offizielle Bedarfsplanung



Prävalenzadjustierter Bedarfsindex



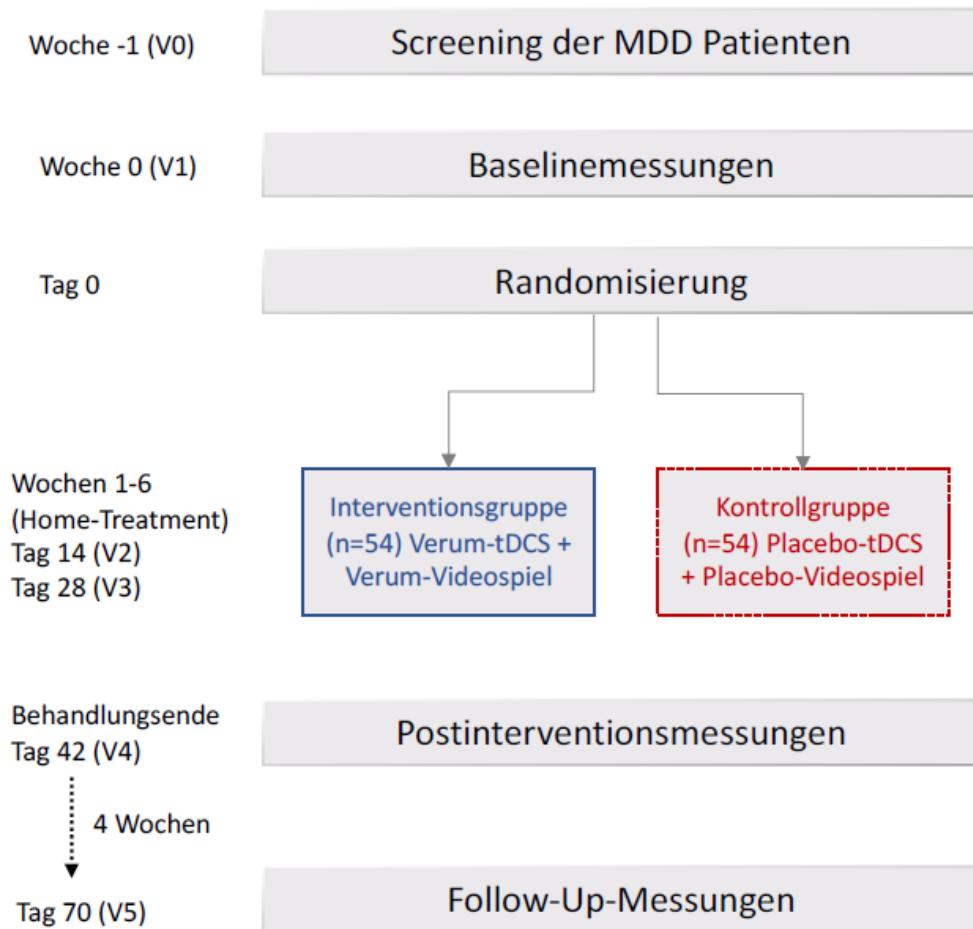
< 14 (43)	≥ 14 - < 16 (39)
≥ 16 - < 18 (58)	≥ 18 - < 20 (83)
≥ 20 - < 26 (63)	≥ 26 (85)

< 14 (143)	≥ 14 - < 16 (32)
≥ 16 - < 18 (41)	≥ 18 - < 20 (98)
≥ 20 - < 26 (2)	≥ 26 (55)

< 14 (0)	≥ 14 - < 16 (0)
≥ 16 - < 18 (3)	≥ 18 - < 20 (229)
≥ 20 - < 26 (139)	≥ 26 (0)

Quelle: IGES auf Grundlage von Daten zur Bedarfsplanung sowie DEGS1-MH-Daten und INKAR-Daten

| BertelsmannStiftung



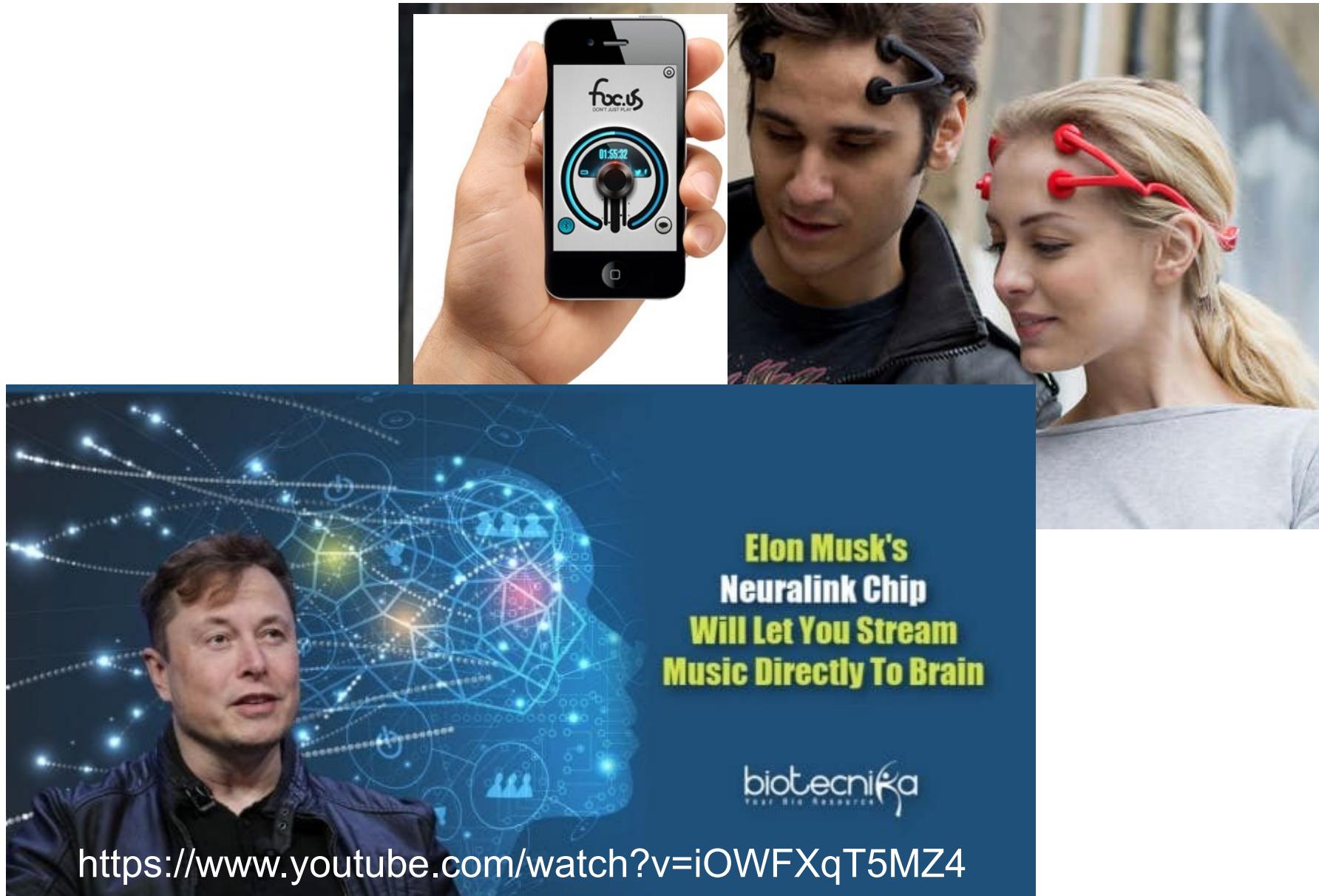
The DiSCoVeR Project: Cognitive control videogame and home-based, self- administered tDCS in MDD

Abb. 2 Studiendesign. Nach dem Screening auf Studieneignung (V0) erfolgt die Baselinephase (V1) und randomisierte Zuteilung entweder zur Interventionsgruppe (Verum-tDCS + Verum-Videospiel) oder zur Kontrollgruppe (Placebo-tDCS + Placebo-Videospiel). Während der Akutbehandlungsphase (6 Wochen Home-Treatment) finden alle zwei Wochen Interimsmessungen statt (V2, V3). Am Behandlungsende (V4) und vier Wochen nach der Behandlung (V5) erfolgen die Postinterventions- und Follow-Up-Messungen.

Zusammenfassung

- tDCS Entwicklung als „neues“ Hirnstimulationsverfahren seit 2000
- Grundsätzlich anderes Wirkprinzip als bei der rTMS, aber ebenfalls Stimulation präfrontaler Hirnregionen
- Klasse I Evidenz? Datenlage noch heterogen: Drei große ($N>100$) randomisierte kontrollierte klinische Studien, davon in zwei Studien signifikante Überlegenheit der tDCS im Vergleich zu einer sham tDCS.
- Positive Meta-Analysen (aber noch kritische Bewertung dieser Evidenzebene)
- Bislang keinen Eingang in die S3-Leitline für Depression
- Potential der tDCS: Sehr nebenwirkungsarme, kostengünstige und für viele Settings (inklusive Home Treatment) geeignete Methode, gute translationale Forschungsmöglichkeiten
- Weitere tES-Formen: tACS, tRNS

Science or Science Fiction?



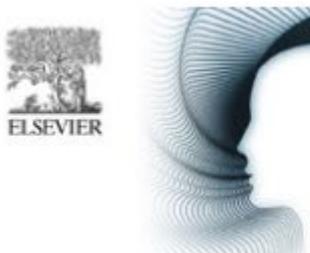


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Bundesministerium
für Bildung
und Forschung

DLR Projektträger

Danke für Ihre Aufmerksamkeit!



4TH INTERNATIONAL
BRAIN STIMULATION
CONFERENCE

Charleston, South Carolina
USA
6–9 December
2021

www.elsevier.com/events/conferences/international-brain-stimulation-conference